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Division of American Home Products Corporation

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March 26, 1999

U.S. REGULATORY AFFAIRS

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket No. 98D-1266

Dear Sir or Madam:

Wyeth-Ayerst Laboratories, a Division of American Home Products Corporation, respectfully submits comments to Docket No. 98 D- 1266 regarding the **draft** guidance entitled "Guidance for Industry, Placing the Therapeutic Equivalence Code on Prescription Drug Labels and Labeling."

Wyeth-Ayerst Laboratories is a major research-oriented pharmaceutical company with leading products in the areas of women's health care, cardiovascular disease therapies, central nervous system drugs, anti-inflammatory agents, vaccines and generic pharmaceuticals, American Home Products Corporation is one of the world's largest research-based pharmaceutical and health care products companies, and is a leading developer, manufacturer and marketer of prescription drugs and over-the-counter medications.

We acknowledge the Agency's position that placing therapeutic equivalence codes together with innovator product names on generic prescription drug labels is intended to "help promote the purpose of the Orange Book, to assist the health professional in product selection and to serve state health agencies in the administration of their drug product selection laws."¹ However, we believe the placement of therapeutic equivalence codes and innovator brand names on generic prescription drug labels is not only unnecessary to achieve the Agency's intended goals, but will have numerous disadvantageous results, and may even cause certain drug products to be misbranded, We therefore request that the Agency rescind the subject draft guidance. Support for our position is herein described,

¹ "Guidance for Industry, Placing the Therapeutic Equivalence Code on Prescription Drug Labels and Labeling," page 5.

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Inclusion of therapeutic equivalence codes on prescription drug labels will render rest) ective labels false and misleading. causing the product to be misbranded.

The therapeutic equivalence rating of a generic product is, and has been, frequently used in promotional labeling and journal advertisements for generic products. Notation of therapeutic equivalence rating is, and has been, considered by the FDA a claim that is a representation of the product. As the Agency is aware, an AB therapeutic equivalence rating means that a generic product is pharmaceutically equivalent to the reference listed drug, and it will have the same clinical effect and safety profile.³ By FDA's own practice, this claim necessitates the inclusion of risk, or fair balance, information in the respective promotional message, since the notation of therapeutic equivalence causes the promotional item to be outside the scope of a reminder message.⁴ The subject draft guidance has not required the inclusion of risk/fair balance information on respective container/carton labels that include therapeutic equivalence codes and references to brand names. Moreover, it would clearly be impractical for most labels to include such information. In our view, therefore, this would cause the drug to be misbranded under the provisions of 21 CFR 201.

In addition, there could be circumstances where a generic product is AB rated to an innovator product for most, but not all, indications. This could happen, for example, if an innovator product had or obtained Waxman-Hatch exclusivity for a new indication. In such a case, placing an AB rating on the generic drug label is inconsistent with the exclusivity obtained under Waxman-Hatch. Such a label would be misleading and the drug therefore misbranded if it suggested that a product was AB rated to the innovator product when in fact the generic product did not have all of the innovator's indications. It is not sufficient to suggest that this is no different than the information in the Orange Book, as the Orange Book itself contains the full list of drug exclusivities. We note as well that the 18th edition of the Orange Book requires almost 20 pages of single-space text to explain the therapeutic equivalence codes, an explanation that would be lacking on drug labels containing such codes under the guidance. Finally, the guidance fails to describe any obligation for generic products to include therapeutic inequivalence ratings where they exist. This may also raise concerns about false and misleading labeling, as the failure to include such information could clearly suggest equivalence.

Further, in those situations where multiple generic products exist, a generic label would be false and misleading if all therapeutically equivalent products available were not noted on a respective label. This is also relevant to situations where multiple branded products exist.⁵

²i, e., products contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration [Approved Prescription Drug Products with Therapeutic Equivalence Evaluations List, the *Orange Book*].

³Approved Prescription Drug Products with Therapeutic Equivalence Evaluations List, the *Orange Book*. 21 CFR 201.100 (f) and 21 CFR 202.1 (e)(2)(i).

⁵For example, Triphasil-21[®], marketed by Wyeth-Ayerst, and Trivora-21[®], marketed by Watson Laboratories, are branded products that are AB rated to each other. Another example is Alesse[®], marketed by Wyeth-Ayerst, and Levlite[®], marketed by Berlex Laboratories. These two products have the same quantitative active ingredients, but are BX rated. However, the guidance would allow each

Inclusion of numerous product names, branded and/or generic, on any prescription drug label will lead to intrinsic confusion on the part of both pharmacist and consumer (see below).

Most importantly, Wyeth-Ayerst believes it would be false and misleading to dispense generic drug products to consumers that contained mention of the innovator product name and respective manufacturer without a disclaimer regarding their **meaning**.⁶ Consumers are frequently given the manufacturer's immediate container when their prescription is dispensed; oftentimes the pharmacist's label does not cover the manufacturer's, or covers it only partially. Thus, consumers will have opportunity to read the therapeutic equivalence code on a label, as well as the name of the innovator manufacturer. This will always be apparent, for example, on unit-of-use packages such as oral contraceptives. The average consumer is not a learned intermediary, and does not know what "AB to product X" means. They may believe they are taking the innovator product, or a product made by the innovator manufacturer, at the least. They may be confused about which manufacturer made the product they are taking, since both the innovator manufacturer and the generic manufacturer will be declared on the same label, and they are far more likely to recognize the innovator name. This is inherently misleading, and also has implications regarding reporting of adverse reactions and liability claims.

Placement of therapeutic equivalence codes and innovator drug names on prescription drug labels is not necessary to enhance generic substitution of products.

Pharmacists already have systems in place to aid in their selection of therapeutically equivalent products. These systems include formulary lists specific to a pharmacist's respective state and/or affiliation (e.g., state formulary lists, hospital or managed care organization formulary, or pharmacy benefit management participation), which are maintained electronically or as hard copy.

The decision to substitute a generic product is thus more complicated than knowledge that an AB rated product exists. Substitution decisions are usually dictated by a combination of formulary lists, pharmacy inventory (which is often limited), and a physician decision that substitution is allowed. The placement of therapeutic equivalence codes on prescription drug labels will not enhance the ability of a pharmacist to substitute generic products, since formulary lists and physician direction are prime contributors towards this action. Inclusion of therapeutic equivalence codes on prescription drug labels is therefore not necessary to enhance generic substitution. Given their inherent, potentially misleading nature, FDA's decision to permit their use is clearly not justified,

respective label to mention the "other" product as well as the BX rating, which will contribute to confusion on the part of the pharmacist and/or consumer, as noted elsewhere in this submission.

⁶ Such a disclaimer should state "AB to Product X means that (name of generic product) is considered therapeutically equivalent to Product X. Therapeutically equivalent means that (name of generic product) and Product X are pharmaceutically equivalent (both products have the same active ingredients in the same strengths, and are of the same dosage form and route of administration) and can be expected to have the same clinical effect and safety profile when administered under conditions noted in product labeling. Please note that (name of generic product) is not manufactured by (name of innovator manufacturer).

Legal Perspectives

We believe the Agency's rationale to allow the use of therapeutic equivalence codes on prescription drug labels is questionable, and in our view, unauthorized by statute as it portends to influence substitution decisions, an area outside of FDA's authority. As stated above, generic drug product promotion has contained claims of therapeutic equivalence rating for many years (accompanied by appropriate risk/balancing information); therefore the legal basis for permitting such claims on a label can not be due to the enactment of the Food and Drug Administration Modernization Act of 1997 with its subsequent repeal of section 301 (1) of the Federal Food, Drug and Cosmetic Act. The Agency's motivation to promote generic products at the expense of innovator products is transparent and outside its statutory mission.

We point out that the use of trademarked names for promotional purposes normally requires contractual agreement with the trademark holder, subject to royalty payments. Companies, including Wyeth-Ayerst, will avail themselves of all resources to protect trademarks. Thus, any use by a generic company of an innovator's trademark on a drug label that is done without contractual agreement constitutes trademark infringement, unfair competition and dilution of the innovator's trademark rights. At the least, the draft guidance should warn that companies who use an innovator's trademark would not be protected from assertion of trademark rights,

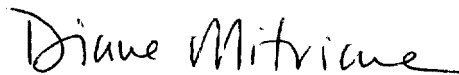
We further note that there are states that prohibit the inclusion of an innovator product name on a respective generic product label,⁷ in order to minimize confusion to the pharmacist and the consumer.

Concluding Remarks

We appreciate the opportunity to provide comments on FDA's "Guidance for Industry, Placing the Therapeutic Equivalence Code on Prescription Drug Labels and Labeling." We respectfully request this guidance be rescinded, since it espouses labeling that is false and misleading, and will cause drug products to be misbranded.

Sincerely,

WYETH-AYERST LABORATORIES



Ms. Diane Mittrione

Senior Director

U. S. Regulatory Affairs

⁷South Dakota and Wisconsin.

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